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Invited review

Role of BDNF epigenetics in activity-dependent neuronal plasticity

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is a key mediator of the activity-dependent processes in the brain that have a major impact on neuronal development and plasticity. Impaired control of neuronal activity-induced BDNF expression mediates the pathogenesis of various neurological and psychiatric disorders. Different environmental stimuli, such as the use of pharmacological compounds, physical and learning exercises or stress exposure, lead to activation of specific neuronal networks. These processes entail tight temporal and spatial transcriptional control of numerous BDNF splice variants through epigenetic mechanisms. The present review highlights recent findings on the dynamic and long-term epigenetic programming of BDNF gene expression by the DNA methylation, histone-modifying and microRNA machineries. The review also summarizes the current knowledge on the activity-dependent BDNF mRNA trafficking critical for rapid local regulation of BDNF levels and synaptic plasticity. Current data open novel directions for discovery of new promising therapeutic targets for treatment of neuropsychiatric disorders.

This article is part of the Special Issue entitled 'BDNF Regulation of Synaptic Structure, Function, and Plasticity'.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a central player in neuronal plasticity and the development of different neurological and psychiatric disorders. Impaired regulation of BDNF expression has been implicated in mood and anxiety disorders, early-life adverse experience and aging, cognitive and neurodegenerative diseases (Autry and Monteggia, 2012; Boulle et al., 2012; Erickson et al., 2012; Frielingsdorf et al., 2012; Mahan and Ressler, 2012; Roth and Sweatt, 2010). BDNF is involved in neurogenesis, neuronal survival and differentiation and long-term potentiation (Hall et al., 2000; Jones et al., 1994; Schwartz et al., 1997). Studies in BDNF-null mice or mice with the Val66Met polymorphism have demonstrated that BDNF is a key regulator of plasticity, dendritic arborization, learning and memory and synaptic morphogenesis (Abidin et al., 2008, 2006; Soliman et al., 2010).

Rodent and human BDNF genes have multiple untranslated 5′-exons; every single 5′-exon is normally spliced to one coding exon with two different 3′-UTRs (untranslated region), resulting in dozens of possible BDNF transcripts variants, each of which encodes an identical BDNF protein (Aid et al., 2007; Liu et al., 2005; Pruunsild et al., 2007). On rare occasions human BDNF transcripts might consist of multiple (up to 3) 5′-exons and one coding exon (Pruunsild et al., 2007), however the molecular mechanisms of these exceptional alternative splicing events are not studied. Importantly, all 5′-exons and both 3′-UTRs are under the control of their own regulatory elements, providing the cells with an exceptional molecular device that can be controlled in an activity-dependent, stimulus-specific temporal and spatial manner (Aid et al., 2007; An et al., 2008; Chiaruttini et al., 2008; Hong et al., 2008; Pruunsild et al., 2007, 2011).

The responsiveness of BDNF to multiple cellular signaling pathways underlines its physiological function in the activity-regulated neuronal network. Moreover, several environmental stimuli, as will be discussed in this review, lead to long-term epigenetic control of BDNF expression. The variations in BDNF levels between cells/individuals/disease states may result not only from genetic polymorphism but also from altered epigenetic programming. Indeed, the genome is not a one-dimensional linear DNA sequence that defines a genotype. A DNA helix is folded into several layers of highly organized chromatin structure to form a chromosome. Knowing the sequence of a protein-coding region of a gene is insufficient for understanding its functioning because chromatin structure dramatically affects gene expression. The actual genome (or epigenome) is an active cooperation of 1) genotype, 2) chromatin modifications (DNA methylation and histone

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modifications) and 3) genetic elements (non-coding RNAs, such as microRNAs; transposable elements), driven by the dynamic environment. Here I will review the main epigenetic modifications that may lead to reprogramming of BDNF expression within differentiated non-dividing neurons or may be potentially inherited by dividing brain cells without changes in the BDNF gene sequence per se.

The main concept of the present review is that dynamic variation in BDNF expression and the subsequent changes in brain functioning and neuronal plasticity are under tight environmental control. Specific focus is paid to those epigenetic changes that drive the activity-dependent alterations in BDNF transcripts levels, temporal or spatial, critical for neuronal plasticity, development of diseases and their treatments. Particularly, this review highlights the recent work on the epigenetic regulation of the BDNF gene that occurs in adult animals or humans, although some key findings on BDNF reprogramming during critical periods of postnatal development and in neuronal cell cultures are also discussed to provide better insight into the molecular mechanisms of the epigenetic control of BDNF expression.

2. Impact of DNA methylation on BDNF expression

DNA methylation is a fundamental epigenetic mechanism for gene silencing throughout lifespans (Bird, 2002; Reamon-Buettner and Borlak, 2007). DNA methyltransferases (DNMT) catalyze the transfer of a methyl group from a donor S-adenosylmethionine to a cytosine at position C5, resulting in a new nucleotide 5-mC, 5-methylcytosine, generally in the context of CpG dinucleotides (Fig. 1) (Lister and Ecker, 2009). The vast majority of CpGs in mammalian genomes are methylated and contribute to the formation of condensed heterochromatin (Bird, 2002). In contrast, hypomethylated CpG sites are located mostly in the CpG islands (CG-rich DNA regions) in close vicinity to genes promoters (Bird et al., 1985; Weber et al., 2007). In dividing cells, *maintaining* DNMT1 recognizes the hemi-methylated CpG site, which is generated during DNA replication, and controls the correct incorporation of a methyl group into newly synthesized DNA strands, copying the methylation pattern from mother to daughter cells (Bird, 2007). In addition to the *maintaining* DNMT1, the methyltransferases DNMT3a and DNMT3b are the key enzymes processing *de novo* DNA methylation independent of DNA replication. *De novo* DNA methylation together with DNA demethylation are predominantly thought to be implicated in neuronal plasticity (Levenson et al., 2006; Nelson et al., 2008).

2.1. BDNF and methylated DNA-binding proteins: case of MeCP2

How does the DNA methylation state at promoter regions affect the level of gene expression? Methylated CpG sites are identified by specific methyl-CpG-binding proteins (Nan et al., 1997; Ng et al., 2000; Prokhortchouk et al., 2001; Skene et al., 2010; Wade et al., 1999) that modify chromatin structure through the recruitment of transcriptional repressor complexes (Fig. 1) (Yoon et al., 2003; Zhang et al., 1999). Mutations in methyl-CpG-binding protein 2 (MeCP2) are associated with Rett syndrome (RTT), a severe progressive neurological disorder characterized by autistic behavior, mental retardation and motor dysfunction (Amir et al., 1999). Patients with RTT begin to present the characteristics of the disease only after 6–18 months of age (Hagberg et al., 1983). A similar phenotype is observed in the mouse models of RTT, MeCP2-mutant or null mice, which grow normally until 5–6 postnatal weeks of age (Chen et al., 2001; Guy et al., 2001). Thus, the development of RTT has been attributed to the lack of MeCP2 function in adult neurons (Luikenhuis et al., 2004; Skene et al., 2010) and glial cells (Ballas et al., 2009; Diaz de Leon-Guerrero et al., 2011; Maezawa et al., 2009).

Accumulating evidence suggests that aberrant regulation of activity-dependent BDNF expression largely contributes to the neuronal phenotype observed in RTT: abnormalities in dendritic

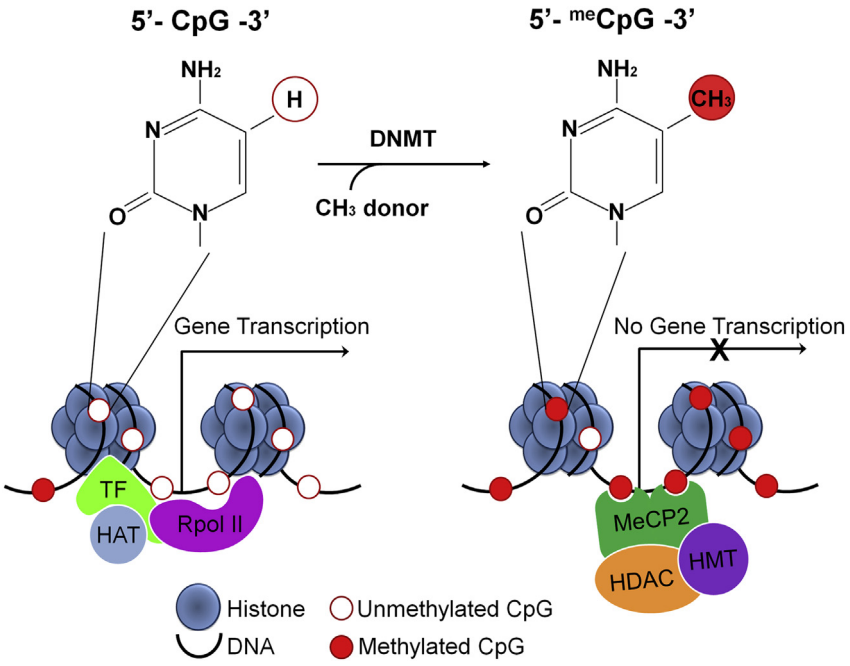

Fig. 1. DNA methylation at gene promoter region. The transfer of a CH3-group from the methyl donor S-adenosylmethionine to the cytosine in the CpG dinucleotide sequence is catalyzed by DNA methyltransferases, DNMT. Low DNA methylation level is correlated with the increased gene transcription level through the binding of transcription factors, TF, histone acetylases, HAT, and RNA polymerase II, Rpol II, to promoter region (left). Increased amount of methylated CpG sites recruits methylated DNA-binding proteins, such as MeCP2, and a chromatin silencing complex that contains histone deacetylases, HDAC, and histone methyltransferases, HMT, resulting in the repressed gene transcription (right).

branching (Chen et al., 2001; Kishi and Macklis, 2004), spine maturation (Zhou et al., 2006), altered excitatory synaptic plasticity (Moretti and Zoghbi, 2006) and increased inhibition (Dani et al., 2005). Interesting, although MeCP2 has been suggested to act as a global chromatin regulator (Skene et al., 2010), BDNF has been found to be selectively regulated by MeCP2 in response to neuronal activity (Chen et al., 2003; Martinowich et al., 2003; Zhou et al., 2006). More specifically, an environmental stimulus, such as the membrane depolarization of cultured neurons, induced a calcium influx and consequent MeCP2 phosphorylation (Tao et al., 1998), which in turn decreased the binding of MeCP2 to methylated CpGs at the activity-dependent BDNF promoter IV (Aid et al., 2007), thus facilitating BDNF transcription (Chen et al., 2003; Martinowich et al., 2003). It has been recently shown that the loss of activity-dependent phosphorylation of MeCP2 not only increased BDNF exon IV expression but also improved synaptogenesis, long-term potentiation (LTP) and spatial memory in mice (Li et al., 2011). Taken together, the mechanism of epigenetic regulation of the BDNF gene by the repressor MeCP2 suggests enhanced BDNF expression in the absence of MeCP2. However, MeCP2 deficiency in RTT, both in humans and mice, results in the down-regulation of BDNF brain level (Chang et al., 2006). Moreover, the morphology of MeCP2-deficient neurons has been shown to be rescued by BDNF overexpression (Larimore et al., 2009). The complex multiple-promoter structure of the BDNF gene itself would suggest a potential mechanism for such discrepancy. Indeed, several recent studies noted the importance of neuronal activity-dependent transcription from the BDNF promoter I, one of the targets of a neuronal gene repressor REST (RE1-silencing transcription factor, also known as neuron-restrictive silencing factor, NRSF) (Abuhatzira et al., 2007; Bruce et al., 2004; Hara et al., 2009; Tian et al., 2009). Together, these studies support the idea that in healthy mature neurons, the REST gene is essentially repressed by MeCP2 and that transcription from both BDNF promoters I and IV is actively but differentially regulated (Pruunsild et al., 2011). In contrast, in the absence of MeCP2 in Rett syndrome, REST is over-expressed, thus inhibiting the induction of BDNF I transcription in response to neuronal activity (Abuhatzira et al., 2007; Hara et al., 2009). Although a number of additional factors may be implicated in neuropathology of MeCP2 deficiency, it would be of great interest to determine whether deregulation of activity-dependent transcription from the BDNF promoter I plays a key role in the aberrant neuronal phenotypes observed in the patients with Rett syndrome.

2.2. BDNF DNA methylation and neurological disorders

Neuronal activity induces dynamic DNA methylation changes in the BDNF gene region. Increased DNA methylation at the promoter area normally promotes a state of transcriptional repression (Robertson and Wolffe, 2000; Suzuki and Bird, 2008) through repressive chromatin remodeling governed mainly by methyl-CpG-binding proteins (Bird, 2002; Klose and Bird, 2006). Environmental stimuli may alter the levels of DNA methylation and consequently gene expression, generating long-lasting cellular memories. Interestingly, dynamic demethylation specifically at the CREB-binding site in the avian BDNF promoter region and elevated binding of phospho-CREB to that promoter in the hypothalamus have been associated with thermal conditioning during the critical period for sensory development in chicks (Yossifoff et al., 2008). Associative learning during fear conditioning promoted dynamic DNA methylation at the BDNF locus in the hippocampus of adult rats (Lubin et al., 2008). Importantly, differential activation of hippocampal BDNF exons I and IV via decreased DNA methylation has been suggested to be a key mechanism in discriminating between associative (fear conditioning) versus non-associative (context learning) long-term memories (Lubin et al., 2008).

Emerging evidence suggests that elevated BDNF exon IV DNA methylation is a mechanism for BDNF down-regulation in adverse environmental circumstances. Traumatic stress experience, such as continuous psychosocial stress, induced hypermethylation of the BDNF IV region and reduced the BDNF expression in the dorsal CA1 area of the hippocampus in PTSD-like rats (Roth et al., 2011). Increased DNA methylation at the BDNF promoter IV in the hippocampus of adult mice has been correlated with depression-like behavior (Onishchenko et al., 2008). Moreover, prolonged light deprivation in adult rats induced repressive methylation at the BDNF promoter IV both in the visual cortex and hippocampus (Karpova et al., 2010), suggesting a molecular mechanism that may predispose light-deprived animals to the depression-like behavior and stress (Gonzalez and Aston-Jones, 2008). Furthermore, recent findings on post-mortem brain samples from suicide completers has revealed significant hypermethylation at specific CpG sites in the BDNF IV region and a concomitant decrease in BDNF messenger RNA in the Wernicke area compared with samples from nonsuicidal subjects (Keller et al., 2010). Changes in the genome-wide level of DNA methylation have not been detected in suicide individuals, implicating an epigenetic gene-specific pattern in the Wernicke area in the pathology of suicide behavior (Keller et al., 2010). Following these studies, it would be of interest to also investigate the potential correlation between DNA methylation levels at the BDNF promoter I in the brain and the development of neurological diseases. Recently, Fuchikami et al. (2011) demonstrated that the DNA methylation profile of a CpG island at the BDNF promoter I, but not IV, in human blood may serve as a valuable diagnostic tool for major depressive disorder. This study suggests an important prospect for identifying new epigenetic biomarkers of neuropsychiatric disorders to improve the classification system, which is currently based on clinical symptoms.

2.3. DNA methylation is reversible

Recent research highlights that the abnormal DNA methylation found in numerous disorders of the nervous system may be potentially responsive to environmental changes, such as nutrition, physical activity or pharmacological treatments. Although DNA methylation patterns at specific gene loci may remain stable over long periods and serve as a basis for the development of the diseases, DNA methylation is a dynamic and reversible process. DNA demethylation may be induced by inhibition of *maintaining* DNMT1 during mitotic DNA replication (Szyf, 2007). DNMT inhibitors, the nucleoside analogues 5-aza-cytidine and 5-aza-2-deoxycytidine, mimicked the behavioral effects of the antidepressant imipramine in adult mice and rats through a dose-dependent inhibition of BDNF DNA methylation in the hippocampus (Sales et al., 2011). Moreover, the DNMT inhibitor zebularine has been shown to induce exon-specific BDNF expression through DNA demethylation mechanisms in the rat hippocampus (Lubin et al., 2008). In this study, Lubin et al. (2008) implicated hippocampal NMDA receptor activation in the epigenetic enhancement of BDNF transcription and contextual fear memory because NMDA receptor blockade by MK801 prevented decreased DNA methylation levels around the BDNF promoter IV.

Although the DNMT inhibitors potentially implicate the dividing glial cells and neurogenesis in reduction of DNA methylation levels under some environmental conditions; however, rapid demethylation of specific genes in the mammalian brain in response to environmental signals is most likely to involve active replication-independent mechanisms. Evidence for existence of a specific DNA demethylase that may directly remove the methyl

group from 5-mC is controversial (Bhattacharya et al., 1999; Ng et al., 1999) and current knowledge suggests a key role of the base excision repair machinery in active DNA demethylation (Zhu, 2009). Tet methylcytosine dioxygenases (TET) convert 5-mC to 5-hmC, 5-hydroxymethylcytosine, that can be further deaminated by AID/APOBEC, activation-induced cytidine deaminase/apolipoprotein B mRNA editing enzyme catalytic polypeptide, to produce a DNA mismatch that is then repaired by the base excision repair machinery (Zhu, 2009). TET1 (Tahiliani et al., 2009) has been recently shown to induce DNA demethylation specifically at the neuronal activity-dependent BDNF and FGF1B promoters regions through oxidation-deamination mechanism (Guo et al., 2011). These studies highlight a potential sensitivity of BDNF expression to altered environmental conditions through its dependence on changes in oxygen levels.

A neural activity-dependent member of the DNA repair machinery, growth arrest DNA-damage-inducible beta (GADD45b), has been implicated in the activity-induced site-specific removal of methyl groups from the BDNF locus, neurogenesis and neural plasticity (Gavin et al., 2012; Ma et al., 2009). Induction of GADD45b by LY379268, a brain-permeable mGlu2/3 (metabotropic glutamate receptor) agonist, reduced DNA methylation levels at the promoters of genes for reelin, BDNF and glutamate decarboxylase 67 and reversed defects in social interaction in adult mice pretreated with the methyl group donor (Matrisciano et al., 2011). These findings implicated epigenetic mechanisms in the efficacy of the mGlu2/3 agonists as antipsychotic agents (Conn et al., 2009; Gewirtz and Marek, 2000).

Age- or nutrition-associated decreases in nicotinamide adenine dinucleotide (NAD) levels have been suggested to provide a critical link between the decelerated cellular metabolism and decreased BDNF signaling that might contribute to cognitive impairment (Chang et al., 2010). Interestingly, in cortical neurons with low NAD levels, the amount of DNA methylation has been elevated at the BDNF promoter IV, leading to BDNF silencing, and, in contrast, increased NAD concentration restored the BDNF level (Chang et al., 2010). A critical role in the NAD-dependent regulation of BDNF expression through chromatin remodeling has been attributed to the binding of the DNA methylation–sensitive factor CTCF associated with cohesin (Chang et al., 2010), mutations in which are thought to trigger severe mental retardation (Dorsett, 2009). Neuronal activity, stimulated by voluntary exercise, has been associated with induced hypomethylation at the BDNF IV region and increased BDNF expression via the MeCP2-dependent pathway in adult rats (Gomez-Pinilla et al., 2011), underlining the potential molecular mechanism for the positive effects of exercise on mental health.

3. Histone modifications at BDNF promoters

Methylated DNA-binding proteins represent a direct link between DNA methylation and histone modifications. For instance, MeCP2 recruits a co-repressor protein complex that contains histone-modifying enzymes such as histone deacetylases (HDAC) (Fig. 1). This complex leads to transcriptional silencing through the formation of a “closed” local chromatin structure (Nan et al., 1997). Nuclear DNA in eukaryotes is wrapped around the core nucleosomal complex consisting of a histone octamer (Kouzarides, 2007). Histones are subjects to posttranslational covalent modifications, the majority of which occur at the N-terminal unfolded tails of the four core histones (H2A, H2B, H3 and H4). Distinct histone modifications influence the accessibility of the transcription factors to DNA by regulating the association of the histone tail with the ATP-dependent chromatin remodeling complex (Kouzarides, 2007). Moreover, the particular combinations of histone modifications around a gene form a “histone code” that specifies the time- and cell type-dependent pattern of gene expression (Jenuwein and Allis, 2001), resulting in a “loss-of-function” or “gain-of-function” gene phenotype without alterations in the DNA sequence (Szyf, 2007). Generally, histone modifications are permissive or repressive for gene transcription (Fig. 2). For instance, acetylation of lysines (or “K” in the single amino-acid code) is associated with the activation of gene transcription, whereas lysine methylation mostly serves as a mark of gene silencing with the exception of modifications of a few specific lysines (Li et al., 2007).

3.1. BDNF activation through histone acetylation

Histone acetyl transferases (HATs) in a complex with their cofactor (acetyl-coenzyme A) catalyze the lysine acetylation that neutralizes the basic charge of tight DNA-histone interactions. In contrast, histone deacetylases (HDACs) mediate the removal of the acetylation mark, resulting in the formation of DNA that is less accessible to transcription factors (Kouzarides, 2007; Lee and Workman, 2007).

Drug abuse has been consistently shown to affect neuronal activity through epigenetic mechanisms. Kumar et al. revealed histone-specific acetylation in response to acute or chronic cocaine administration. Acute cocaine increased histone H4 acetylation at the cFos and FosB promoters, whereas chronic cocaine induced the sustained acetylation of histone H3 at the BDNF and Cdk5 promoters in the rat striatum (Kumar et al., 2005). This result was similar to the effect of chronic electroconvulsive seizures in the hippocampus (Tsankova et al., 2004). Activation of a permissive chromatin state and phospho-CREB protein binding to the BDNF promoter IV in the rat prefrontal cortex has been implicated in cocaine-induced neuronal plasticity (Sadri-Vakili et al., 2010). In contrast, cocaine abstinence promoted histone H3 acetylation and the consequent increase in BDNF I transcription in the ventral tegmental area (Schmidt et al., 2012). Epigenetic activation of the BDNF I transcription level in the ventromedial prefrontal cortex (vmPFC) through acetylation of histone H3 has been associated with the successful extinction of aversive memories of morphine withdrawal (Wang et al., 2012). The authors showed that extinction training could be potentiated by an intra-vmPFC infusion of the HDAC inhibitor trichostatin A (TSA) and by increased CREB protein binding to the acetylated BDNF promoter (Wang et al., 2012).

Emerging evidence suggests that epigenetic reprogramming of BDNF by chronic cocaine intake may not only alter neuronal and behavioral phenotype in the cocaine-addicted male rats but also could be transmitted to their next generation (Vassoler et al., 2013). In this study, chronic cocaine induced histone H3 acetylation at the BDNF promoters I, IV and VI in the sperm of addicted rats. Interestingly, their male, but not female, offspring showed a cocaine-resistant phenotype associated with the increased BDNF transcription level and histone H3 acetylation specifically at the BDNF promoter IV in the prefrontal cortex (Vassoler et al., 2013). Although the mechanisms of conservation of this histone mark has not been investigated and may involve additional epigenetic changes in DNA/histone methylation (Santos et al., 2005) at the BDNF locus, this study highlights a possibility for the transgenerational maintenance of the BDNF epigenetic state.

Proper histone acetylation levels have been shown to affect LTP and long-term memories (Alarcon et al., 2004). For instance, increased histone H4 acetylation around BDNF promoters I and IV in the prefrontal cortex contributed to improved extinction of conditioned fear in mice (Bredy et al., 2007). Moreover, the HDAC inhibitor valproic acid (VPA) enhanced not only the extinction of cued fear memory but also its acquisition and reconsolidation (Bredy and Barad, 2008). Interestingly, a single exposure to

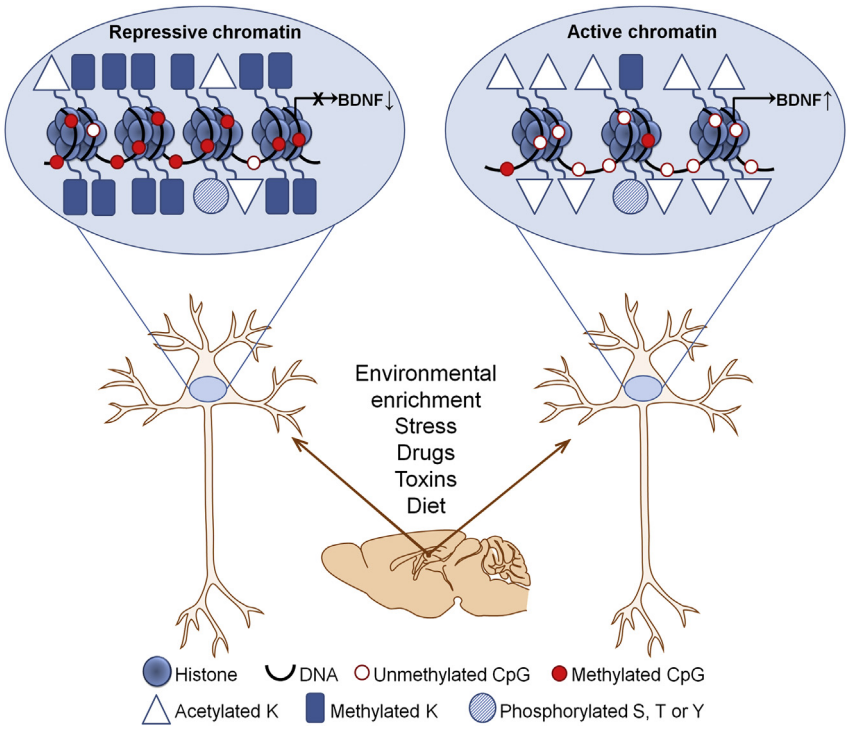

Fig. 2. Histone modifications at BDNF promoters. Different environmental stimuli affect the DNA methylation pattern and lead to the formation of the repressive (more condensed) or active (more open) chromatin structure, resulting in the decreased or increased gene transcription, respectively. Histone acetylation (open triangle) at lysine, K, is an epigenetic imprint of transcriptionally active chromatin, whereas histone methylation (closed blue box) is mostly associated with repressed chromatin. Phosphorylation (patterned circle) at serine, S, threonine, T, or tyrosine, Y, is generally linked to gene activation.

prolonged stress before fear conditioning in rats increased acetylation of histones H3 and H4 at the activity-dependent BDNF promoters I and IV and heightened the hippocampal levels of BDNF transcription, thus strengthening the subsequent consolidation of fear memories (Takei et al., 2011). This study suggests a molecular mechanism for the elevated long-lasting traumatic fear memories in patients with PTSD.

Recently, several studies have reported an HDAC inhibition effect of some antidepressants as well as mood- and cognition-enhancing effects of HDAC inhibitors. In particular, hyperacetylation at the BDNF promoters IV and VI (nomenclature adapted to (Aid et al., 2007)) and selective down-regulation of HDAC5 by the chronic tricyclic antidepressant imipramine restored the hippocampal BDNF expression, which had been decreased by chronic social defeat stress in mice (Tsankova et al., 2006). Accordingly, the administration of the selective serotonin reuptake inhibitor (SSRI) fluoxetine to adult mice promoted histone H3 acetylation at the promoter BDNF IV and reversed depression-like behavior, which had been induced by perinatal exposure to an environmental contaminant, methylmercury (Onishchenko et al., 2008). Interestingly, neither imipramine nor fluoxetine altered the repressive histone methylation status induced by stressful conditions (Onishchenko et al., 2008; Tsankova et al., 2006). Importantly, both fluoxetine and the HDAC inhibitor TSA have been shown to reactivate visual cortical plasticity in adult rats, promoting a transient increase in BDNF expression through histone hyperacetylation at its promoters (Maya Vetencourt et al., 2011). This study also highlighted a critical role for the 5-HT(1A) receptor and BDNF signaling pathway in establishing a plastic state in the visual cortex because local infusion of the 5-HT(1A) receptor antagonist WAY-100635 into the visual cortex prevented permissive histone remodeling at the BDNF promoters and reactivation of visual cortical plasticity (Maya Vetencourt et al., 2011).

An epigenetic strategy for treating impaired synaptic plasticity and cognitive declines during aging has been suggested by Zeng et al. (2011). Using hippocampal slices from young and aged rats, the authors showed a robust decline in LTP and dendritic spine number and a significant decrease in BDNF expression and signaling in aged animals. The reduction in BDNF coincided with hypoacetylated states of histone H3 and/or H4 at essentially all BDNF promoters. However, short-term treatment of hippocampal slices with TSA or sodium butyrate not only promoted an increase in H3/H4 acetylation levels but also restored the LTP and spine density to the levels observed in young animals (Zeng et al., 2011). It would be of great interest to investigate whether this enhanced synaptic plasticity induced by acute HDAC inhibitors has a long-lasting effect on cognitive improvement.

3.2. Histone methylation effects on BDNF expression

Histone methyltransferases (HMTs) and demethylases (HDMTs) catalyze histone methylation and demethylation, respectively, at lysine or arginine residues. Activation of gene transcription is associated with increased methylation of histone H3 at lysine 4 (H3K4) and at lysine 36 (H3K36); however, the majority of other methylation events at histone residues H3K9, H3K14, H3K27, and H4K20 at gene promoters normally mediate transcriptional inactivation (Kouzarides, 2007). For instance, incorporation of the methyl moiety from a methyl-donor, S-adenosylmethionine, to histone residues H3K27 and H3K4 is catalyzed by different HMT complexes, the Polycomb (PcG) silencing complex and the Trithorax (TrxG) activating complex, respectively (Papp and Muller, 2006). The tri-methylated H3K27me3 variant has been shown to mediate transcriptional repression by inhibiting the deposition of activating histone acetylation marks that are important to form an “open” chromatin state (Schuettengruber et al., 2007).

Adverse environmental conditions may reduce BDNF expression through repressive histone H3 methylation at the BDNF promoters in rodent brains (Karpova et al., 2010; Onishchenko et al., 2008; Tsankova et al., 2006). In contrast, a positive environmental influence, such as environmental enrichment, has been shown to produce opposite changes. Indeed, 3–4 weeks of mouse exposure to an enriched environment significantly increased hippocampal BDNF expression through complex histone remodeling at its promoters (Kuzumaki et al., 2011). Activating histone marks (methylated H3K4) at promoters III and VI were elevated, whereas repressive methylation of H3K9 and H3K27 were markedly decreased at promoters III and/or IV (Kuzumaki et al., 2011). Complex regulation of BDNF and other plasticity-related genes levels by histone methylation has been critically involved in fear memory formation (Gupta et al., 2010), implicating the G9a/GLP histone methyltransferase complex in the regulation of neuronal connectivity during the consolidation of long-term fear memories (Gupta-Agarwal et al., 2012). Interestingly, viral overexpression of the HMT G9a in the critical brain reward region, the nucleus accumbens, after chronic cocaine administration repressed local BDNF signaling and rendered mice less vulnerable to subsequent stress (Covington et al., 2011), see also (Maze et al., 2010). In contrast, acute nicotine exposure significantly down-regulated the G9a/GLP complex in the mouse cortex and, subsequently, reduced the H3K9me2 histone mark at the BDNF promoters, thus activating BDNF expression (Chase and Sharma, 2012). Gaining more insight into the mechanisms of action of the HMT complex G9a/GLP could identify new potential therapeutic targets for treatments of mood and addictive disorders.

4. Post-transcriptional regulation of BDNF mRNA levels and trafficking

Rapid synapse-specific responses to environmental stimuli have a critical role in the fine tuning of neuronal plasticity. Activity-dependent mRNA targeting and protein synthesis in dendrites suggest a mechanism for rapid local regulation of the activity of plasticity-related molecules such as BDNF (Bramham and Wells, 2007; Tongiorgi et al., 1997). The multiple-promoter structure of BDNF and BDNF splice variants with different 5′ and 3′-UTRs (Fig. 3) serve as excellent and complex cellular tools not only for the temporal neuronal response to distinct stimulating cues but also for the differential spatial distribution of BDNF transcripts (Aid et al., 2007; An et al., 2008; Chiaruttini et al., 2008, 2009; Pruunsild et al., 2007).

4.1. 5′-Exons mediated BDNF mRNA trafficking

Studies in neuronal culture showed that BDNF transcripts targeting to dendrites might be promoted by a constitutively active element in the protein-coding region, while multiple 5′-UTRs with either inhibitory or permissive signals for dendritic targeting controlled the transcript-selective trafficking (Chiaruttini et al., 2009). Indeed, BDNF splice variants with exons I and IV were

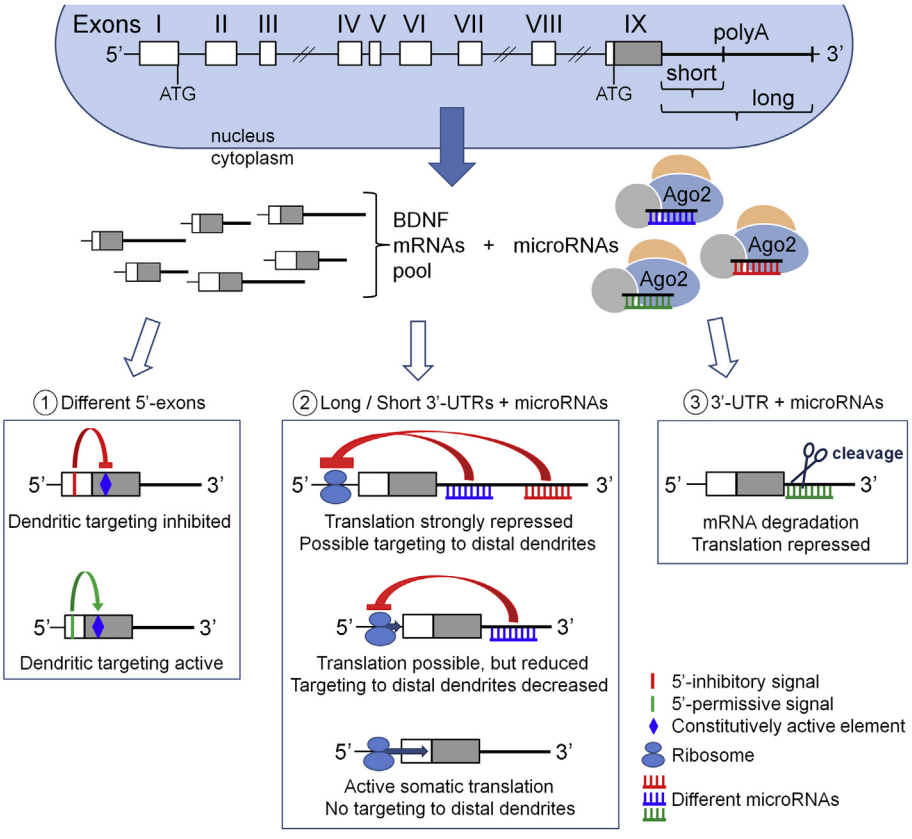

Fig. 3. Post-transcriptional regulation of BDNF transcripts. Nucleus: Structure of the rodent BDNF gene (adapted from Aid et al., 2007) consists of multiple 5′ untranslated exons I–VIII (open boxes) and one coding exon IX (gray box). ATG, start codon that indicates initiation of transcription. 3′-UTR of BDNF transcripts is composed of either short or long polyA tail. Cytoplasm: Different BDNF transcripts are translated into protein or targeted to the distal cellular compartments (distal dendrites) for the local translation later on. The dendritic targeting may be regulated by the inhibitory or permissive signals (located in exons), short or long 3′-UTRs and multiple regulatory microRNAs (bound to the Ago2-protein complex). Particular microRNAs binding to the BDNF 3′-UTR may result in the repression of the local translation into BDNF protein and, thus, in dendritic targeting of BDNF mRNAs or in the BDNF transcripts degradation.

restricted to the proximal dendrites and cell soma, whereas transcripts containing exon II or IV were found in more distal cellular compartments (Chiaruttini et al., 2008, 2009). Moreover, dendritic targeting through a constitutively active element in the coding region was mediated by an RNA-binding protein Translin, and its interaction with BDNF mRNA was blocked by the G196A (or Val66Met) mutation (Chiaruttini et al., 2009). Thus, in addition to the impaired BDNF protein vesicular release for the Val66Met polymorphism (Chen et al., 2005), this mutation may also compromise mRNA trafficking to distal dendrites. These findings implicate improper BDNF sorting in the learning and memory impairments and susceptibility to mood disorders of Met allele carriers (Chen et al., 2006; Krishnan et al., 2007; Soliman et al., 2010).

4.2. BDNF dendritic targeting by its 3′-UTR

The activity-dependent trafficking of specific BDNF transcripts is further regulated by the inducible signals located in the 3′-UTR. BDNF mRNAs with the short 3′-UTR have been shown to be mostly concentrated and translated in the cell soma to maintain the basal level of the BDNF protein. In contrast, the long 3′-UTR-containing transcripts were targeted to dendrites, where their translation may be robustly up-regulated upon neuronal activation (An et al., 2008; Lau et al., 2010). Importantly, targeting to dendrites appears to be associated with the *cis*-acting translation suppressor located in the long BDNF 3′-UTR (Lau et al., 2010). Furthermore, different types of environmental stimuli, such as KCl-induced depolarization in rat hippocampal neurons, have also been shown to activate the dendritic trafficking of the transcripts with the short 3′-UTR (Oe and Yoneda, 2010). A novel critical link between BDNF and energy balance has been determined by Liao et al. (2012). The researchers showed that the local dendritic translation of BDNF mRNA with the long 3′-UTR could be stimulated by leptin and insulin in rodent hypothalamic neurons. This study implicated dendritic localization and local BDNF protein synthesis in the control of feeding behavior and susceptibility to obesity (Liao et al., 2012).

4.3. MicroRNA control of BDNF transcripts

Local dendritic translation and mRNA stability are primarily thought to be regulated by microRNAs (Fig. 3). The BDNF 3′-UTR has been predicted to contain up to 20 binding sites for microRNAs from 13 families (Wu et al., 2010). Key components of the microRNA maturation machinery offer a tool for modulating BDNF expression. In the nucleus, the long hairpin-containing transcript for microRNA is processed by RNase III Drosha into double-stranded pre-microRNA that is exported to the cytoplasm (Heo and Kim, 2009). In the cytoplasm, RNase III Dicer cleaves and removes the hairpin loop and processes the pre-microRNA into 21- to 23-nucleotide duplexes, generating mature microRNAs. Then, mature microRNAs in a complex with the Argonaute protein bind to the targeted mRNAs in a sequence-specific manner to cleave them or suppress their translation (Bartel, 2009). A conditional knockout of the Dicer1 gene in an adult mouse forebrain produced a massive loss of the brain-specific microRNAs, resulting in increased BDNF translation, spine morphogenesis and memory enhancement (Konopka et al., 2010). Moreover, huntingtin, a key protein implicated in the pathogenesis of Huntington's disease, has been shown to be associated with the transporting neuronal granules that contain BDNF mRNA and the Argonaute2 complex (Ma et al., 2010). Although more *in vivo* data are required, this finding suggests a role of huntingtin and/or the microRNA processing complex-mediated transport of BDNF transcripts in the development of Huntington's disease.

The effect of particular microRNAs in the post-transcriptional control of BDNF expression is now beginning to be elucidated (Caputo et al., 2011; Lee et al., 2012; Miura et al., 2012), and an inspiring strategy for treatments of specific neurological disorders has already been suggested. Indeed, the repressive function of a microRNA, miR-206, on BDNF expression through binding its 3′-UTR (Miura et al., 2012) has been up-regulated in Alzheimer disease, both in a transgenic Tg2576 mouse model and in humans (Lee et al., 2012). However, intra-ventricle injection or intra-nasal administration of an antagomir (AM206, an inhibitor of miR-206) not only increased the BDNF levels in the brains of the Tg2576 mice but also prevented dendritic spine degeneration and memory impairments (Lee et al., 2012). This study suggests the possibility of using non-invasive approaches to treat such devastating neurodegenerative disorders as Alzheimer disease.

5. Conclusions

The BDNF gene is regulated by neural activity in a temporal and spatial manner. The cellular-compartment, cell-type and tissue-specific epigenetic pattern of the BDNF gene critically differs from that of its genetic polymorphisms. The studies exploring the gain-of-function (e.g., systemic/local overexpression) or loss-of-function (e.g., full/conditional knockout) methodologies do not provide complete information about the role of BDNF in active processes in the brain, such as neuronal differentiation or survival, migration or spine development (Hong et al., 2008). Acquiring better knowledge on the epigenetic regulation of such a complex-structured gene as BDNF would promote the development of more safe and effective treatments for neurological and psychiatric disorders.

The epigenetic state of the BDNF gene might not necessarily change its expression levels at a given time point but may underline a predisposition to mood, addictive or neurodegenerative disorders, as well as non-responsiveness to treatment strategies, when triggered by aversive environmental conditions. The epigenome is dynamic and specific environmental manipulations, such as pharmacological or psychological (behavioral in animals) therapies, could direct the epigenetic reprogramming of a disease state toward recovery. It's important to warn, however, that current epigenetic pharmacological treatments affect the functioning of the whole epigenome. Although the use of the epigenetic drugs such as DNMT, HDAC or microRNA inhibitors is growing, the selectivity of these drugs in restoring the epigenetic pattern of only the particular genes implicated in the pathogenesis of disease is largely unstudied at this point. To prevent potential harmful (cytotoxic or carcinogenic) effects of these drugs on cell/tissue functioning throughout the body, thorough research should be performed to discover therapeutically beneficial agents with limited side effects.

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